CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-323/S-021

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

K1.1

K1.1

N20323

N20323

Vivelle

(estradiol transdermal system)

2EC.
3/2/00
2:02 pm

0.0375, 0.05, 0.075, 1.0 mg/day

11.0, 14.5, 22.0, 29.0 cm^2

NDA 20-323
Efficacy Supplement 21

Novartis

PM: Moore

Primary UF Goal Date:
March 3, 2000

Secondary UF Goal Date:
May 3, 2000

Volume 1 of 1

NOVARTIS

Distributed by
Novartis Pharmaceuticals Corporation
East Hanover, NJ 07936

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20323	**Trade Name:**	VIVELLE ESTRADIOL TRANSDERMAL SYSTEM
Supplement Number:	21	**Generic Name:**	ESTRADIOL
Supplement Type:	SE8	**Dosage Form:**	
Regulatory Action:		**Proposed Indication:**	Treatment of moderate-to-severe vasomotor symptoms associated with the menopause Treatment of vulval and vaginal atrophy Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, Pediatric content not necessary because of pediatric waiver

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)

____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Does Not Apply
Formulation Status	-
Studies Needed	-
Study Status	-

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

This supplement does not qualify for a pediatric exclusivity as it is not a new dosage form, new indication, new chemical entity, new route of administration or new dosing regimen. The dosage is already approved. The clinical data presented revises the labeling to remove the reference to a delayed onset of efficacy. February 25, 2000.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, DIANE MOORE

/S/ 2/25/00

Signature Date

NOVARTIS

ORIGINAL

SUPPL NEW CORRESP

S-021-NC

June 18, 1999

Lisa Rarick, MD
Acting Director
Division of Reproductive and Urological
Drug Products/HFD-580
Office of Drug Evaluation II
Attn: Document Control Room 17B-20
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 20-323
Vivelle®(estradiol transdermal system)

Amendment to a Pending Supplement

Dear Dr. Rarick:

Reference is made to our Supplemental New Drug Application to Vivelle (estradiol transdermal system) NDA 20-323 (S-021), dated April 30, 1999. The supplement is to revise the current labeling, to remove the restrictive language in the Dosage And Administration Section of the labeling that states that some women taking the 0.0375 mg/day dosage may experience a delayed onset of efficacy.

In addition, reference is made to a request from Ms. Diane Moore, Project Manager, on June 15, 1999, to submit revised language for the debarment certification statement to comply with the Draft Guidance for Industry: Submitting Debarment Certification Statements, dated September 1998.

At this time Novartis Pharmaceuticals Corporation hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with the application referenced above.

If you have any questions or comments concerning this submission, please contact me at (973) 781-3665.

Sincerely yours,

Lynn Mellor

Lynn Mellor
Associate Director
Drug Regulatory Affairs

Attachments: Form 356h

Submitted in duplicate

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

D/F

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: 2/11/00

From: Lana L. Pauls, M.P.H. LP 2/11/00
Associate Director, Division of Reproductive and Urologic Drug Products, HFD-580

Subject: Review of financial disclosure documents for NDA 20-323/S-021

To: the file (NDA 20-323)

I have reviewed the information provided and find that it is acceptable. In addition, all studies in support of approval of this application were completed prior to February 2, 1999.

cc:
Orig NDA 20-323
HFD-580/DMoore

20-323/S-021

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. XXXX-XXXX
Expiration Date: XX/XX/XX

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a ~~significant equity in the sponsor as defined in 21 CFR 54.2(b)~~ did not disclose any such interests. ~~I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).~~

Clinical Investigators	see attached.	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Peter Richardson, MD	TITLE Vice President Bone/Respiratory
FIRM/ORGANIZATION Novartis Pharmaceuticals Corporation	
SIGNATURE P.C. Richardson	DATE 2/22/99

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Please DO NOT RETURN this form to this address.

FORM FDA 3454 (10/98)

EF

Created by Electronic Document Services/USDHHS: (301) 443-2454

All studies were completed prior to February 2, 1999 therefore, the crossed out statements within (1) are not applicable.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. XXXX-XXXX
Expiration Date: XX/XX/XX

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a ~~significant equity in the sponsor as defined in 21 CFR 54.2(b)~~ did not disclose any such interests. ~~I further certify that no listed investigator was the recipient of significant payments of other sorts as defined~~ in 21 ~~CFR 54.2(f).~~

Clinical Investigators		
	see attached.	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)), and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Peter Richardson, MD	TITLE Vice President Bone/Respiratory
FIRM/ORGANIZATION Novartis Pharmaceuticals Corporation	
SIGNATURE P.C. Richardson	DATE 2/22/99

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Please DO NOT RETURN this form to this address.

FORM FDA 3454 (10/98) EF

Created by Electronic Document Services/USDHHS: (301) 443-2454

All studies were completed prior to February 2, 1999 therefore, the crossed out statements within (1) are not applicable.

Novartis Pharmaceutical Corporation

DSI Audit of Clinical Studies

No clinical studies were audited because the product has previously been approved and only one new study was submitted for review. It was determined by the Medical Officer that no clinical study audit was needed.

Vivelle® (estradiol transdermal system) 0.0375, 0.05, 0.75, 0.1 mg/day
Novartis Pharmaceutical Corporation

DSI Audit of Clinical Studies

No clinical studies were audited because the product has previously been approved and only one new study was submitted for review. It was determined by the Medical Officer that no clinical study audit was needed.

/S/
2/24/00

/S/
2/24/00

Division Director Memorandum
New Drug Application

NDA#:	20,323/S-021
Sponsor:	Novartis Pharmaceuticals Corporation
Drug:	Vivelle® (Estradiol Transdermal System)
Indication:	Treatment of moderate to severe vasomotor symptoms associated with menopause; treatment of vulvar and vaginal atrophy; treatment of hypoestroestrogenism due to hypogonadism, castration or primary ovarian failure
Dose:	0.0375 mg per day; 0.05 mg per day; 0.075 mg per day; 0.1 mg per day
Formulation:	Transdermal patch
Date of submission:	April 30, 1999
Date of memorandum:	February 24, 2000

Background

Vivelle® was originally approved by the FDA as a transdermal patch system for estrogen replacement therapy on October 28, 1994. The product was approved in four strengths as noted above. As described in the primary and secondary clinical reviews for the current application, the originally approved labeling for this product contained restrictive language specific to the 0.0375 mg per day dose, noting that a delayed onset of efficacy may occur with the 0.0375 mg per day dose patch.

The current application contained data from a randomized, double-blind, parallel group study (i.e., Protocol 036) comparing the Vivelle® 0.0375 mg per day patch to a placebo patch for the treatment of moderate-to-severe vasomotor symptoms associated with menopause. In addition, the sponsor performed a retrospective analysis of data from one of the two phase 3 trials (i.e., study 1003-A) contained in the original NDA submission for this product upon which initial

approval of the product was based. During the original review cycle for this product, study 1003-A showed that the 0.0375 mg per day dose of Vivelle® was not statistically significantly better than placebo in reducing the number of hot flushes women experienced during the last two weeks of cycle 1. However, the second phase 3 trial contained in the original NDA submission (i.e., study 1003-B) did support the efficacy of the 0.0375 mg per day Vivelle® patch for the indication sought.

Per the FDA Guidance Document on the clinical evaluation of estrogen- and estrogen/progestin-containing drug products for hormone replacement therapy, the primary efficacy analysis for these trials should show both a clinically and statistically significant reduction in the frequency *and* severity of hot flushes in the treated groups compared with the control groups. This reduction should occur within 4 weeks of treatment initiation and should be maintained throughout 12 weeks of treatment. The primary endpoint for protocol 036 was the change from baseline in the mean number of hot flushes per day during the last two weeks of the first treatment cycle. The secondary endpoint for the study focused on the change in the severity of hot flushes at the end of each treatment cycle. As described in the primary and secondary clinical reviews and the statistical review, the results of this study demonstrated a statistically significant reduction in the mean number of hot flushes for the Vivelle® 0.0375 mg/day patch as compared to placebo. As described further in the primary clinical and statistical reviewer's memos dated February 23 and February 24, 2000 respectively, the study results also demonstrated that the Vivelle® 0.0375 mg per day patch was statistically and clinically significantly better than placebo in reducing the severity of hot flushes experienced by trial participants. Both the reduction in the number of hot flushes and in their severity occurred within 4 weeks of treatment initiation and was maintained throughout 12 weeks of treatment. Thus, the safety and effectiveness of the Vivelle® 0.0375 mg per day patch for the treatment of moderate-to-severe vasomotor symptoms was demonstrated in this study. This data was deemed sufficient to recommend approval of this application.

Recommendations:

I concur with the conclusions of the primary and secondary clinical reviewers and the statistical reviewer and recommend that this application be approved. I also recommend that the previous restrictive language specific to the 0.0375 mg per day dose of Vivelle® regarding delayed onset of efficacy be removed.

/S/ 2/24/00

Susan S. Allen, MD, MPH
Acting Director, HFD-580

Cc: NDA 20-323
HFD-580/Allen/Slaughter/Price
HFD-103/Houn/Raczkowski

Group Leader Memorandum
Vivelle®

NDA:	**20-323**
Drug:	**Vivelle®**
Dosage Form/Route:	**Transdermal patch**
Strength:	**0.0375 mg per day**
Applicant:	**Novartis Pharmaceuticals Corporation**
Original Submission Date:	**April 30, 1999**
Date of Memorandum:	**December 21, 1999**

In this application, the Sponsor is seeking approval to remove the following statement from the label for Vivelle®: "Some women taking the 0.0375 mg/day dosage may experience a delayed onset of efficacy". This statement was included in the label, because there was a discrepancy between the two trials in the original NDA with respect to the efficacy of the 0.0375 dose. The largest study, 1003A, did not support the efficacy of the 0.0375 mg/day dose, while the smaller of the two trials, 1003B, did. In support of the request to remove the above statement from the current label, the Sponsor has submitted Study 036 a randomized, double-blind, parallel group study comparing Vivelle® 0.0375 mg/day to placebo for the treatment of moderate-to-severe vasomotor symptoms. The results of this study demonstrate that the 0.0375 mg/day dose is both safe and effective for the treatment of vasomotor symptoms with the effectiveness demonstrated by week 4 and maintained through week 12. I concur with the recommendation of the primary reviewer that this application should be approved.

The agreed upon label is included in this action package. The label contains a figure that presents the efficacy of the 0.0375 mg/day dose for the treatment of vasomotor symptoms at 4, 8 and 12 weeks. While it is stated that all doses of Vivelle® (0.0375 mg, 0.05 mg, 0.075 mg, and 0.1 mg) are effective for the control of vasomotor symptoms, the 0.0375mg/day dose is the recommended starting dose.

/S/ 2/01/3/00

Shelley R. Slaughter, MD, Ph.D.
Reproductive Medical Team Leader, HFD-580

MEMO TO THE FILE

Date: February 23, 2000

Subject: NDA 20-323-S021

Name of Drug: Vivelle

Sponsor: Novartis Pharmaceuticals Corporation

Clinical Indication: Relief of Vasomotor Symptoms

Comments:

As has been the policy of this division (HFD-580-) and the Estrogen-Progestin Draft Guidance document, sponsors when treating vasomotor symptoms have been required to show relief of symptoms for both the frequency and severity of vasomotor symptoms.

In my formal review, tables 1 and 2 showed the Mean number of Hot flushes per 24 hours in the last two weeks of cycle 1. The sponsor did not originally supply in tabular form the frequency of hot flush data. This data was later imputed by the statistical reviewer, Sobhan Maboob, Ph.D and placed in his review and my original review. In the final review of this supplement, questions have been raised as to whether the sponsor has data that showed improvement in the baseline severity of Hot flushes per 24 hours. The following table, compiled by Sobdan Maboob addresses this concern:

Mean Change (SD) for Baseline in Severity of Hot flushes/24 hours

		Week 4		Week 8		Week 12
Treatment	n	Mean (SD)	n	Mean (SD)	N	Mean (SD)
Vivelle	128	-1.33 (.87)	129	-1.63 (.94)	124	-1.78 (.92)
Placebo	125	-0.70 (.75)	120	-0.88 (.85)	118	-0.94 (.88)
P-value		$p < 0.05$		$p < 0.05$		$p < 0.05$

As demonstrated in previous reviews of HRT products, severity data supports frequency data seen in the original review at the end of Cycle 1.

Phill H. Price, M.D.

NDA 20-323/S-021
Vivelle
Novartis

Regarding the labeling comments from the clinical and statistical reviews (i.e., black box WARNING, Clinical Studies section, INDICATIONS AND USAGE section, CONTRAINDICATIONS section, WARNINGS section, PRECAUTIONS section, Pregnancy section, ADVERSE REACTIONS section, and Initiation of Therapy section in the Physician's labeling and the Black Box WARNING, Benefits of Treatment with Vivelle section, WHEN ESTROGENS SHOULD NOT BE USED section, DANGERS OF ESTROGENS section, and SIDE EFFECTS section), the labeling submitted by the sponsor on February 4, 2000, is acceptable.

/S/

2/17/00

ORIGINAL

NOVARTIS

Lynn Mellor
Associate Director

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781-3665
Fax 973 781-3590

FEB 1 - 2000

February 7, 2000

Susan Allen, MD
Acting Director
Division of Reproductive and Urological
Drug Products/HFD-580
Office of Drug Evaluation II
Attn: Document Control Room 17B-20
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 20-323 (S-021)
Vivelle®(estradiol transdermal system)

General Correspondence

NDA SUPP AMEND

(SNC-021)

Dear Dr. Allen:

Reference is made to the Vivelle (estradiol transdermal system) efficacy supplement (S-021). The supplement is for a labeling change to remove restrictive language, regarding vasomotor symptoms associated with the menopause, that some women taking the 0.0375 mg/day dosage may experience a delayed onset of efficacy.

In addition, reference is made to our teleconference with the Division on January 18, 2000 to discuss the draft labeling for the above-mentioned supplement. Attached for your information is a copy of our meeting minutes. At this time we are requesting a copy of the meeting minutes issued by the Division.

If you have any questions or comments concerning this submission, please contact me at (973) 781-3665.

Sincerely yours,

Lynn Mellor

Lynn Mellor
Associate Director
Drug Regulatory Affairs

Vivfda10.doc

Submitted in duplicate

REVIEWS COMPLETED

☐ MEMO

DATE

ORIGINAL

NDA SUPP AMEND

S-021-021-B2

NOVARTIS

Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973-781 7500
Fax 973-781 6325

February 4, 2000

Susan Allen, MD
Acting Director
Division of Reproductive and Urological
Drug Products/HFD-580
Office of Drug Evaluation II
Attn: Document Control Room 17B-20
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 20-323 (S-021)
Vivelle® (estradiol transdermal system)

Labeling Supplement – Draft Labeling

Dear Dr. Allen:

Reference is made to the teleconference with the Division on January 18, 2000, to discuss the draft labeling for the Vivelle (estradiol transdermal system) efficacy supplement (S-021). The supplement is for a labeling change to remove restrictive language, regarding vasomotor symptoms associated with the menopause, that some women taking the 0.0375 mg/day dosage may experience a delayed onset of efficacy.

In addition, reference is also made to FDA communications on January 20, January 27, February 1 and February 2, 2000.

The Vivelle labeling has been revised based on discussions and comments received from the Division. One particular comment, at the January 18, 2000 teleconference, concerned deletion of the paragraph in the Clinical Pharmacology Section of the draft label that discussed the hepatic first pass effect. As requested the reference to the hepatic first pass effect has been deleted from the label. However, we wish to reiterate that the label for Climara® (estradiol patch) does contain information on the hepatic first pass effect and that the agency stated it is their intention to have the language concerning the hepatic first pass effect removed from the Climara® labeling.

Attached is the draft Vivelle labeling. Also included in this submission is an electronic file containing the labeling. We are submitting the document in Portable Document Format (PDF) on a diskette, in the archival copy. In addition a desk copy is being provided that contains the document in Word format on one diskette and in PDF on a

second diskette. The diskettes provided have been virus scanned using Network Associates VirusScan version 4.0.3a (formerly known as McAfee Virus Scan). The diskettes were found to be virus free.

In addition, a copy of the draft annotated labeling is included as a reference that identifies the revisions. The draft annotated label is provided as a paper copy only.

We appreciate your review of our draft labeling at your earliest convenience. If you have any questions or comments concerning this submission, please contact me at (973) 781-3665.

Sincerely yours,

Lynn Mellor

Lynn Mellor
Associate Director
Drug Regulatory Affairs

Vivfda9.doc

Draft labeling: 4 copies

Desk copy: Ms. Diane Moore, Project Manager / HFD-580

Copy: Regina Brown, NJ District Pre-Approval Inspection Coordinator

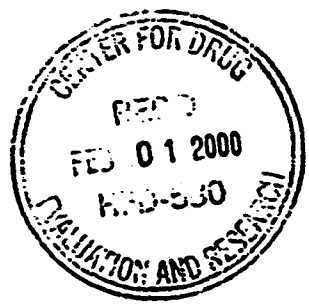
REVIEWS COMPLETED
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

NOVARTIS

Lynn Mellor
Associate Director

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781-3665
Fax 973 781-3590



January 24, 2000

Susan Allen, MD
Acting Director
Division of Reproductive and Urological
Drug Products/HFD-580
Office of Drug Evaluation II
Attn: Document Control Room 17B-20
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 20-323
Vivelle® (estradiol transdermal system)

General Correspondence

Dear Dr. Allen:

Reference is made to the Vivelle (estradiol transdermal system) efficacy supplement (S-021). The supplement is for a labeling change to remove restrictive language, regarding vasomotor symptoms associated with the menopause, that some women taking the 0.0375 mg/day dosage may experience a delayed onset of efficacy.

In addition, reference is made to a telephone conversation with Ms. Diane Moore, Project Manager, on January 19, 2000. Ms. Moore requested that we indicate that a Safety Update was not submitted for this efficacy supplement, as there is no new information to provide. The basis of the supplement was a single study (Protocol 36) and an Integrated Summary of Efficacy. Also included was the resubmission of sections of the two pivotal study reports, focusing on efficacy, from the Original NDA. An Integrated Summary of Safety section was not applicable for this supplement, however safety data from Protocol 36 was included in the clinical trial report. Furthermore, in the FDA minutes of the February 4, 1999 teleconference, the content of the supplement as noted above and the plan not to submit an Integrated Summary of Safety was agreed to.

If you have any questions or comments concerning this submission, please contact me at (973) 781-3665.

Sincerely yours,

Lynn Mellor
Associate Director
Drug Regulatory Affairs

Submitted in Duplicate

Vivfda8.doc

NOVARTIS

June 21, 1999

Lisa Rarick, MD
Acting Director
Division of Reproductive and Urological
Drug Products/HFD-580
Office of Drug Evaluation II
Attn: Document Control Room 17B-20
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 20-323/S-017
Vivelle® (estradiol transdermal system)

Response to Request for Information

Dear Dr. Rarick:

Reference is made to your letter dated June 14, 1999, concerning our Vivelle (estradiol transdermal system) NDA 20-323 'Special Supplement – Changes Being Effected' (S-017), dated March 19, 1998, regarding the addition of language concerning venous thromboembolism. As noted in the correspondence this labeling supplement had an implementation date of August 1998.

In a telephone conversation with Ms. Diane Moore, Project Manager, on June 18, 1999, it was agreed that the venous thromboembolism language that the agency requested to be incorporated into the labeling for this product is from the Draft Labeling Guidance for Non-Contraceptive Estrogen Drug Products, dated September 1998. Furthermore, for the Package Insert, this language appears under the WARNINGS section in the Draft Guidance whereas in the June 14, 1999, letter from the agency it was requested to be placed under the PECAUTIONS section of the label.

Under 21 CFR 314.110, we wish to notify you of our intent to file an amendment to the application when the Labeling Guidance for Non-Contraceptive Estrogen Drug Products is finalized, and therefore, mechanisms should not be implemented to withdraw our application pursuant to 21 CFR 314.65.

If you have any questions or comments concerning this submission, please contact me at (973) 781-3665.

Sincerely yours,

Lynn Mellor
Associate Director
Drug Regulatory Affairs

Submitted in duplicate

Attachments: Form 356h

NOVARTIS

Lynn Mellor
Associate Director

Novartis Pharmaceuticals Corporation
Regulatory Affairs
Route 10
East Hanover, NJ 07936-1080

Tel 973 781-3665
Fax 973 781-3590

January 7, 2000

Susan Allen, MD
Acting Director
Division of Reproductive and Urological
Drug Products/HFD-580
Office of Drug Evaluation II
Attn: Document Control Room 17B-20
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 20-323
Vivelle® (estradiol transdermal system)

General Correspondence

NDA SUPP AMEND
SE8-021

Dear Dr. Allen:

Reference is made to the facsimile dated December 21, 1999, from the Division concerning the Vivelle (estradiol transdermal system) efficacy supplement (S-021). The supplement is for a labeling change to remove restrictive language that some women taking the 0.0375 mg/day dosage may experience a delayed onset of efficacy.

The facsimile provides FDA's comments on our draft label. At this time we are submitting an updated annotated draft label based on the comments received from the agency. In the text a number follows each strike out or addition. This number can be referenced in a separate document (attached) where a description of the annotation is provided.

We would like to discuss the updated Vivelle draft label with you at your earliest convenience.

In addition, during a telephone conversation on January 5, 2000 with Ms. Diane Moore, project manager, it was communicated that the Division would prefer a table rather than a figure for representation of the changes in vasomotor symptoms. It was acknowledged that the FDA comments stated that a table or a figure was optional. In the Clinical Studies section we are proposing to represent the changes in vasomotor symptoms in a figure format. It is felt that a graphic representation of the data is more easily understandable than in a table format. Furthermore, the Wyeth-Ayerst estradiol transdermal system has approved labeling that includes representation of vasomotor symptoms in a figure. Novo Nordisk Pharmaceuticals' Activelle™ (estradiol/ norethindrone acetate tablets) approved labeling also includes representation of vasomotor symptoms in a figure.

We would like to bring to your attention that the Protocol 036 intent-to-treat analysis for Weeks 3 & 4 for the primary efficacy variable (the change from baseline in mean number of hot flushes per 24 hours in the last two weeks of Cycle 1) was not done per protocol. This was discussed with the Division during our November 2, 1999 teleconference. Reference is also made to the November 4, 1999 submission, which details this discussion.

The intent-to-treat analysis for Weeks 3 & 4 is currently being validated, with validation complete no later than January 19, 2000. Therefore, the figure presented in the updated annotated label is draft, although we do not expect any change after validation is complete. We will provide an updated figure based on the outcome of the validation of Weeks 3 & 4 upon completion, if necessary.

If you have any questions or comments concerning this submission, please contact me at (973) 781-3665.

Sincerely yours,

Lynn Mellor
Associate Director
Drug Regulatory Affairs

Vivfda7.doc

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

ORIGINAL

NOVARTIS

Lynn Mellor
Associate Director

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781-3665
Fax 973 781-3590

NEW CORRESP
AIC

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
NOV 29 1999
HFD-580

November 23, 1999

Lisa Rarick, MD
Director
Division of Reproductive and Urological
Drug Products/HFD-580
Office of Drug Evaluation II
Attn: Document Control Room 17B-20
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 20-323
Vivelle®(estradiol transdermal system)

General Correspondence

Dear Dr. Rarick:

Reference is made to Vivelle ® (estradiol transdermal system) NDA 20-323 and to a request from Diane Moore, Project Manager, dated October 28, 1999. Ms. Moore requested that we commit to submit a supplement to provide for identifying information (printing) on the backing layer of the Vivelle transdermal system. Furthermore, this information can be submitted as a Special Supplement - Changes Being Effected.

At this time we commit to submit information to support a Special Supplement - Changes Being Effected to provide for identifying information (printing) on the backing layer of the Vivelle transdermal system in July 2000.

If you have any questions or comments concerning this submission, please contact me at (973) 781-3665.

REVIEWS COMPLETED

ACTION:
☐ N.A.I. ☐ MEMO

DATE

Sincerely yours,

Lynn Mellor

Lynn Mellor
Associate Director
Drug Regulatory Affairs

Submitted in duplicate

Attachments: Form 356h

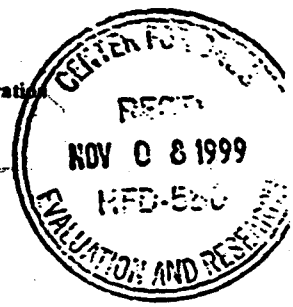
NOVARTIS

ORIGINAL

Eyra Miller
Associate Director

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781-3665
Fax 973 781-3590



NEW CORRESP
NC

November 4, 1999

Lisa Rarick, MD
Acting Director
Division of Reproductive and Urological
Drug Products/HFD-580
Office of Drug Evaluation II
Attn: Document Control Room 17B-20
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 20-323
Vivelle® (estradiol transdermal system)

General Correspondence

Dear Dr. Rarick:

Reference is made to the November 2, 1999 teleconference, between the Division and Novartis, concerning the Vivelle (estradiol transdermal system) efficacy supplement (S-021). The supplement is for a labeling change to remove restrictive language that some women taking the 0.0375 mg/day dosage may experience a delayed onset of efficacy.

FDA participants from the Division included Ms. Moore, Project Manger; Dr. Price, Medical Reviewer; and D. Sobhan, Statistical Reviewer. Participants from Novartis included Ms. Mellor, Regulatory; Dr. Gupta, Medical; and Dr. Gibson, Statistics.

FDA requested a teleconference to determine, in Protocol 036, if an analysis was done for the primary variable (the change from baseline in mean number of hot flushes per 24 hours in the last two weeks of Cycle 1) based on the 257 treated patients to yield results that would be close to the intent-to-treat principle. Novartis indicated no analysis was done using the entire 257 treated patients in Cycle 1.

Novartis clarified how the two analyses reported in the clinical study report on the primary variable were done, and illuminated how these analyses differed from the intent-to-treat principle. Novartis and FDA agreed that a new analysis would be conducted using the 257 treated patients whenever possible and would be acceptable because it would result in an analysis of the primary variable much closer to the intent-to-treat philosophy. This would enable the agency to move forward in their review of the supplement.

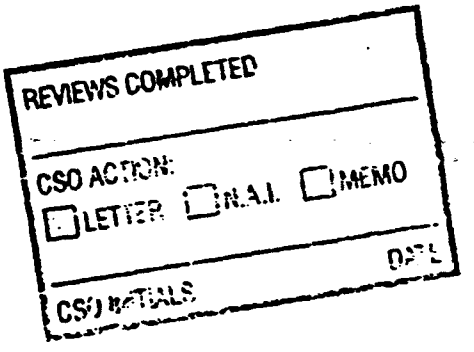
Dr. Sobhan indicated that he could execute the analysis to FDAs satisfaction quickly if directed by Dr. Gibson to the appropriate data sets and variables. In a separate telephone conversation Dr. Gibson directed Dr. Sobhan to the appropriate data sets and variables. Dr. Sobhan indicated that he would perform the analysis and notify Novartis of the outcome.

Attached are specifics regarding the analyses performed for the primary variable in Protocol 036 and the specifics on the approximate intent-to-treat analysis that will be performed.

If you have any questions or comments concerning this submission, please contact me at (973) 781-3665.

Sincerely yours,

Lynn Mellor
Associate Director
Drug Regulatory Affairs



ORIGINAL

NDA SUPP AMEND SE8-021 BL

NOVARTIS

Lynn Mellor
Associate Director

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781-3665
Fax 973 781-3590

September 20, 1999

Lisa Rarick, MD
Acting Director
Division of Reproductive and Urological
Drug Products/HFD-580
Office of Drug Evaluation II
Attn: Document Control Room 17B-20
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 20-323/S-021
Vivelle®(estradiol transdermal system)

Amendment to a pending application

& Proposed Draft Labeling: Geriatric Use

Dear Dr. Rarick:

Reference is made to our Supplemental New Drug Application (S-021) to Vivelle ® (estradiol transdermal system) NDA 20-323 dated April 30, 1999. The supplement is to revise the current labeling to remove the restrictive language in the Dosage and Administration Section of the label that states that some women taking the 0.0375 mg/day dosage may experience a delayed onset of efficacy. In addition, as requested by the agency on February 4, 1999, the Clinical Pharmacology Section of the label was updated in accordance with the Draft Labeling Guidance for Non-Contraceptive Estrogen Drug Products – Physician and Patient Labeling 9/3/98.

At this time we are submitting an amendment to the pending application to make limited revisions in the label to reflect certain aspects of the Draft Labeling Guidance for Non-Contraceptive Estrogen Drug Products – Physician and Patient Labeling 9/8/98, and to add three adverse events reported from post-marketing experience.

In addition, we are also including in this amendment to the pending supplement proposed labeling for the Geriatric Use subsection of the label.

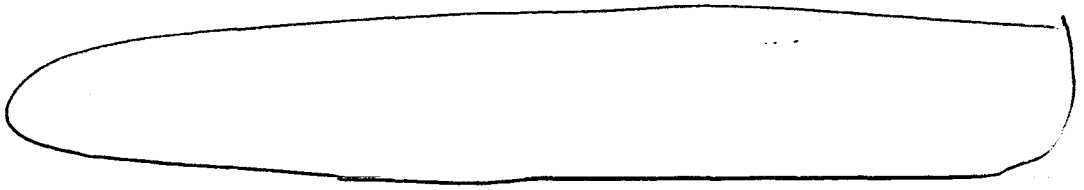
Attached are the revised draft label (Attachment 1) and an annotated draft label (Attachment 2) reflecting these changes. The new proposed changes in the draft annotated label are in Italics and bolded to distinguish the new revisions from the revisions submitted on April 30, 1999. The April 30th revisions are only underlined in the draft annotated label. In addition, the draft label and draft annotated label are provided on a diskette in Word 6.

A Spontaneous Report listing to support the addition of three adverse events reported from post-marketing experience to the 'Adverse Reaction' section of the label is provided in Attachment 3.

Regarding the addition of the 'Geriatric Use' subsection to the label please refer to our NDA 20-323 for Vivelle (estradiol transdermal system), CFR 201.57(f)(10), and to the Final Rule entitled, "Specific requirements on Content and Format of Labeling for Human Prescription Drugs; Addition of 'Geriatric Use' subsection in the Labeling," effective August 27, 1998.

As directed by the Final Rule, we have completed a review of available controlled studies, of information gathered from other studies and experience (including our database of spontaneous adverse drug reaction reports), and of pertinent information from well-documented studies discovered via a literature search. No adequate and well-controlled studies have been conducted in the geriatric population. In addition, the number of patients over 65 years of age enrolled in clinical studies not isolated to geriatric participants is insufficient to permit a generalization regarding limitations or effects of dosing in this population. Also, no significant safety issue in the geriatric population was identified in review of the spontaneous report adverse event rate by age. Further, a review of the medical literature has similarly revealed no findings pertinent to appropriate treatment of geriatric subjects.

Based on these data, we propose the following 'Geriatric Use' subsection be added to the PRECAUTIONS section of the package insert for this product:



In support of this proposal, we are providing a description of the supporting documentation including a complete listing of literature reports reviewed. (Attachment 4).

If you have any questions or comments concerning this submission, please contact me at (973) 781-3665.

Sincerely yours,

Lynn Mellor
Associate Director
Drug Regulatory Affairs

Viveff1.doc

Attachments: -Form 356h

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

NOVARTIS

ORIGINAL

SUPPL NEW CORRESP
S-021-NC

June 18, 1999

Lisa Rarick, MD
Acting Director
Division of Reproductive and Urological
Drug Products/HFD-580
Office of Drug Evaluation II
Attn: Document Control Room 17B-20
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 20-323
Vivelle® (estradiol transdermal system)

Amendment to a Pending Supplement

Dear Dr. Rarick:

Reference is made to our Supplemental New Drug Application to Vivelle (estradiol transdermal system) NDA 20-323 (S-021), dated April 30, 1999. The supplement is to revise the current labeling, to remove the restrictive language in the Dosage And Administration Section of the labeling that states that some women taking the 0.0375 mg/day dosage may experience a delayed onset of efficacy.

In addition, reference is made to a request from Ms. Diane Moore, Project Manager, on June 15, 1999, to submit revised language for the debarment certification statement to comply with the Draft Guidance for Industry: Submitting Debarment Certification Statements, dated September 1998.

At this time Novartis Pharmaceuticals Corporation hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with the application referenced above.

If you have any questions or comments concerning this submission, please contact me at (973) 781-3665.

Sincerely yours,

Lynn Mellor

Lynn Mellor
Associate Director
Drug Regulatory Affairs

Attachments: Form 356h

Submitted in duplicate

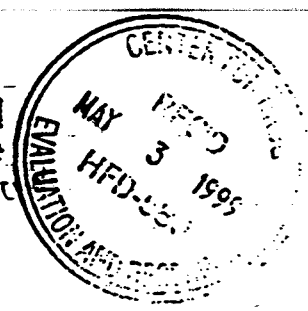
REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

ORIGINAL

NOVARTIS

NDA NO. 20323 REF. NO. SEE-031

NDA SUPPL FOR CITY U.S. ETC.



April 30, 1999

Lisa Rarick, MD
Acting Director
Division of Reproductive and Urological
Drug Products/HFD-580
Office of Drug Evaluation II
Attn: Document Control Room 17B-20
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 20-323
Vivelle® (estradiol transdermal system)

Efficacy Supplement

Dear Dr. Rarick:

We are submitting a Supplemental New Drug Application to Vivelle (estradiol transdermal system) NDA 20-323, to revise the current labeling, to remove the restrictive language in the Dosage And Administration Section of the labeling that states that some women taking the 0.035 mg/day dosage may experience a delayed onset of efficacy.

Reference is made to a pre-meeting package submitted on January 21, 1999, and agreements reached in a February 4, 1999 teleconference with the Division and a subsequent agreement on April 19, 1999. The present supplement includes the clinical trial report for Protocol 036 that confirms the efficacy of the 0.0375 mg/day dose in the treatment of moderate to severe vasomotor symptoms associated with menopause and an Integrated Summary of Efficacy. In addition, the clinical trial reports for Studies 1003-A and 1003-B, the Original Integrated Summary of Efficacy, and the reanalyzes of Study 1003-A that were submitted in the Original NDA application are being resubmitted in this supplement. However, as agreed with the Division selected information from the clinical trial reports is being resubmitted which includes the text of each study report; summary tables for baseline/demographics, primary efficacy variables and the secondary efficacy variable for severity of hot flushes; and the same information for the statistical analyses tables as the summary tables. An Integrated Summary of Safety section is not applicable for this supplement, however safety data from Protocol 036 is included in the clinical trial report.

As noted in our January 21, 1999 correspondence, all Case Report Forms (Protocol 036) for this sNDA which are required under 21 CFR 314.50(f)(2) are only submitted electronically on CD-ROM. Case Report Forms for Studies 1003-A and 1003-B were previously submitted in the Original NDA and are cross referenced to the previous submission. In addition, selected efficacy data files for Study 036 are provided electronically in SAS (version 6.12) as agreed to on February 4, 1999. Also, as requested text files in Word 6 are provided for Protocol 036, the new Integrated Summary of Efficacy, and the draft package insert.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

In addition, the Clinical Pharmacology Section of the labeling has been updated in accordance with the Draft Labeling Guidance for Non-Contraceptive Estrogen Drug Products - Physician and Patient Labeling 9/8/98 as requested by the Division on February 4, 1999.

There is no new Chemistry, Manufacturing and Controls information being submitted in this supplement, therefore a Field Copy will not be provided to the New Jersey District Office.

The FDA User Fee for this application (User Fee ID 3692) was submitted on April 8, 1999.

If you have any questions or comments concerning this submission, please contact me at (973) 781-3665.

Sincerely yours,

Lynn Meller

Lynn Meller
Associate Director
Drug Regulatory Affairs

vivfda.doc

Attachments: Form 356h

Volumes 1-26

Copy of cover letter: Ms. Diane Moore, Project Coordinator, Division of Reproductive and Urological Drug Products

Copy of cover letter: Regina Brown, NJ District Pre-Approval Inspection Coordinator

Minutes of Teleconference

Date: January 19, 2000 **Time:** 1:00 - 1:15 PM **Place:** Parklawn; Diane Moore's Office

NDA: 20-323 **Drug Name:** Vivelle (estradiol transdermal system)

Indication: Hormone Replacement Therapy (HRT)

External Constituent: Novartis Pharmaceuticals Corporation

Type of Meeting: Labeling Guidance (Chemistry)

FDA Lead: Dr. Moo-Jhong Rhee **External Lead:** Ms. Lynn Mellor

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Diane Moore – Regulatory Project Manager, Division of Reproductive and Urologic Drug Product (DRUDP; HFD-580)
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

External Participant:
Lynn Mellor – Associate Director, Drug Regulatory Affairs, Novartis

Meeting Objective:
To discuss the [redacted] in the labeling for the Vivelle label.

Background: Previous labeling contained [redacted] section of the labeling for Vivelle NDA 20-323. [redacted]

Discussion Items:
- the legal established USAN [redacted]
- USP describes the [redacted]

Decisions Reached:
- the tradename, established name, and chemical name should be shown in the labeling
- although other labels currently contain [redacted] been overlooked in the past, but to be consistent, they should all be revised to use the same terminology; [redacted]

- regarding pediatric exclusivity, the sponsor feels that it is not necessary to request a waiver for pediatric studies for this supplement because it falls under one of the listed indications to be granted a waiver, i.e., symptoms of menopause under the Pediatric Final Rule, CFR 314.55(c); this

supplement is not a new indication, a new dosage form, a new chemical entity, a new route of administration or a new dosing regimen and therefore, the rule does not apply hereto. The Division agrees that a request for a waiver for a pediatric study is not necessary for this supplement.

- **Action Items:**

• **Item:**	**Responsible Party:**	**Due Date:**
• discuss proposal [redacted] internally and respond to FDA request	Ms. Mellor	1-week
• respond regarding Clinical Pharmacology section revision proposal	Ms. Mellor	1-week

/S/
Signature, recorder

/S/
Concurrence, Chair

cc:
HFD-580
HFD-580/SAllen/MMann/SSlaughter/PPrice/TRumble/DMoore/MRhee/AMitra
HFD-580/TRumble/DMoore

Concurrence:
TRumble 1.24.00/MRhee 1.28.00

APPEARS THIS WAY
ON ORIGINAL

Minutes of Teleconference

Date: January 18, 2000 **Time:** 2:00 - 2:30 PM **Place:** Parklawn; Rm. 17B43

NDA: 20-323 **Drug Name:** Vivelle (estradiol transdermal system)

Indication: Hormone Replacement Therapy (HRT)

External Constituent: Novartis Pharmaceuticals Corporation

Type of Meeting: Labeling Guidance

FDA Lead: Dr. Shelley Slaughter **External Lead:** Ms. Lynn Mellor

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Marianne Mann, M.D. - Deputy Director, Division of Reproductive and Urologic Drug Product (DRUDP; HFD-580)
Shelley Slaughter, M.D., Ph.D. –Medical Team Leader, DRUDP (HFD-580)
Phill Price, M.D. - Medical Officer, DRUDP (HFD-580)
Diane Moore – Regulatory Project Manager, DRUDP (HFD-580)
Lisa Kammerman, Ph.D. - Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Lisa Stockbridge, Ph.D. - Regulatory Reviewer, Division of Drug Marketing and Communication (DDMAC; HFD-42)

External Participants:
Lynn Mellor – Associate Director, Drug Regulatory Affairs, Novartis
Stephanie Barba – Therapeutic Area, Drug Regulatory Affairs, Head
Eric Gibson, Ph.D. - Statistician
Nathalie Ezzet, Ph.D. - Statistician
Marie Roberts - Clinical
Sonja Pearse, M.D. – Clinical Safety and Epidemiology
Neal Sailer - Marketing

Meeting Objective: To discuss the Vivelle label.

Background: The sponsor sent a telefacsimile dated January 18, 2000, which contained a copy of the sponsor's June 21, 1999, response to the Agency's June 14, 1999, letter regarding the addition of language concerning venous thromboembolism.

Discussion Items:

- the sponsor has agreed to most of the proposed labeling revisions proposed by DRUDP; however, the sponsor objects to the addition to this label of language concerning venous thromboembolism and has submitted a copy of their June 14, 1999, letter in support of that position
-

- the sponsor maintained that they do not have adhesion data, as requested; the sponsor submitted a comment to the 1992 Noncontraceptive Estrogen Labeling Guidance regarding the need for a standardized protocol to collect adhesion data so that the various studies address the same aspect of the issue
- the sponsor included a figure describing changes in vasomotor symptoms at Weeks 3-4, 5-8, and 9-12 in the intent-to-treat (ITT) population in response to the Division's request to include a table or figure describing changes in vasomotor symptoms at Weeks 4, 8 and 12 in the placebo and Vivelle 0.0375 mg arms in the ITT population; the sponsor did not have complete diary data from all patients at baseline and Weeks 3 and 4; therefore, the figure presented represented an average of Weeks 3-4, 5-8, and 9-12
- the baselines in the figure are the average number of hot flushes per day which was 10-12 for placebo and treatment combined
- [redacted]

Decisions Reached:

- comments regarding the thromboembolism subsection of the labeling can be addressed in a subsequent labeling supplement once the 1999 Noncontraceptive Estrogen Labeling Guidance is finalized
- the Chemists will discuss [redacted]
- the 4.4 ± 2.3 half-life for estradiol in the PK section is acceptable
- the **Adhesion** subsection should appear separate from the two adjacent subsections and should be bolded
- a study to analyze adhesion properties of the transdermal system will be required to address the adhesion section of the labeling when the 1999 Estrogen Labeling Guidance is finalized
- DRUDP will supply the sponsor with a copy of the draft Estrogen Guidance for guidance to developing an appropriate adhesion study protocol
- the sponsor's figure representing data averages for Weeks 3-4, 5-8 and 9-12 is not acceptable
- the sponsor will provide the data in the form of a line graph for Weeks 4, 8 and 12
- "standard deviation (SD)" should be incorporated into the title of the figure
- the mean change from baseline values are not on the figure; the raw number of hot flushes are not shown; it is acceptable to not include the raw numbers of hot flushes in the figure, but the baseline should be included in the text under the figure
- the sponsor will provide DRUDP with analyses for figure for review prior to amending the labeling
- in the **Clinical Studies** subsection, the sentence that reads, "All doses of Vivelle (0.0375 mg, 0.05 mg, 0.075 mg, and 0.1 mg) [redacted] for the control of vasomotor symptoms." should be replaced with the following sentence: "All doses of Vivelle (0.375 mg, [redacted], 0.075mg and 0.1 mg) are [redacted] effective for the control of vasomotor symptoms"
- in the **ADVERSE EVENTS** section, the sentence that reads, "Rash was reported [redacted] in these trials." should be revised to read, [redacted] so that the numbers are specific and terms such as [redacted] are avoided
- sponsor will submit a labeling amendment including the revisions as agreed

- **Action Items:**

• **Item:**	**Responsible Party:**	**Due Date:**
• provide DRUDP with analyses for new figure	Novartis	1-2 weeks
• DRUDP to simultaneously analyze data for graph	DRUDP	1-2 weeks
• submit labeling amendment to Supplement 021	Novartis	1-2 weeks

/S/ 2/11/00
Signature, recorder

/S/ 2/14/00
Concurrence, Chair

cc:
HFD-580
HFD-580/SAllen/MMann/SSlaughter/PPrice/TRumble/DMoore/LKammerman/MSobhan
HFD-580/TRumble/DMoore

Concurrence:
TRumble 1.24.00/PPrice, LKammerman 1.27.00/MMann 1.28.00/SSlaughter 1.31.00

Concurrence not received from LStockbridge

Novartis Pharmaceuticals Corporation

Fax

To:	Diane Moore	**From:**	Lynn Mellor
Fax:	301 827-4260	**Pages:**	2
Phone:	301 827-4236	**Date:**	01/18/00
Re:	Vivelle NDA 20-323	**CC:**	

☐ Urgent ☐ For Review ☐ Please Comment ☐ Please Reply ☐ Please Recycle

Dear Diane,

Reference is made to our telephone conversation today. I received your fax which provided for a copy of the FDA June 14, 1999 letter concerinng the hypercoaguability section of the labeling. The language specified is from the 1998 draft labeling guidance. Attached is a copy of a letter from Novartis dated June 21, 1999 in which we indicated or intent to file an amendment to the application when the labeling guidance is finalized.

Sincerely,

Lynn Mellor

Lynn Mellor

NOVARTIS

June 21, 1999

Lisa Rarick, MD
Acting Director
Division of Reproductive and Urological
Drug Products/HFD-580
Office of Drug Evaluation II
Attn: Document Control Room 17B-20
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 20-323/S-017
Vivelle®(estradiol transdermal system)

Response to Request for Information

Dear Dr. Rarick:

Reference is made to your letter dated June 14, 1999, concerning our Vivelle (estradiol transdermal system) NDA 20-323 'Special Supplement – Changes Being Effected' (S-017), dated March 19, 1998, regarding the addition of language concerning venous thromboembolism. As noted in the correspondence this labeling supplement had an implementation date of August 1998.

In a telephone conversation with Ms. Diane Moore, Project Manager, on June 18, 1999, it was agreed that the venous thromboembolism language that the agency requested to be incorporated into the labeling for this product is from the Draft Labeling Guidance for Non-Contraceptive Estrogen Drug Products, dated September 1998. Furthermore, for the Package Insert, this language appears under the WARNINGS section in the Draft Guidance whereas in the June 14, 1999, letter from the agency it was requested to be placed under the PECAUTIONS section of the label

[redacted]

If you have any questions or comments concerning this submission, please contact me at (973) 781-3665.

Sincerely yours,

Lynn Mellor
Associate Director
Drug Regulatory Affairs

Submitted in duplicate

Attachments: Form 356h

Meeting Minutes

Date: December 6, 1999 **Time:** 11:00 AM - 12:00 PM **Place:** Parklawn; Room 17B-45

NDA: 20-323/S-021 **Drug Name:** Vivelle (estradiol transdermal system) 0.0375, 0.05, 0.75, 0.1 mg/day

Indication: Estrogen replacement therapy (ERT)

Sponsor: Novartis Pharmaceuticals Corporation

Type of Meeting: Labeling

FDA Lead: Dr. Shelley Slaughter

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Marianne Mann, M.D. - Deputy Director, Division of Reproductive and Urologic Drug Product (DRUDP; HFD-580)
Shelley Slaughter, M.D., Ph.D. – Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Phill Price, M.D. - Medical Officer, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Diane Moore – Regulatory Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Venkateswar R. Jarugula, Ph.D. -Pharmacokinetic Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Wakel Kamp Barnes Monique, M.D., Ph.D., OCPB HFD 870
Mahboob Sobhan, Ph.D. – Statistical Reviewer, Division of Biometrics II (DBII) @ (HFD-160)

Meeting Objective: To continue discussion of the labeling for Supplement 21.

Discussion Points:

- Chemistry
  - the issue regarding the printed labeling on the actual patch will be addressed in another supplement which will be submitted by the sponsor as a Chemistry supplement to the NDA

Decisions Reached:

- the Agency proposed revisions for the Vivelle labeling supplement S-021 are incorporated into the attached version of the Vivelle label; additions are denoted by <u>double underlines</u> and deletions are denoted by ~~strikeouts~~; comments and requests for further information are delineated by **bolded 14 point font;** (note: figures and chemical structures are not included)
- instead of the present copy of the Information for the Patient from the physician's insert for the patient package insert, a separate patient package insert should be proposed following the plain English initiative with patient friendly language following the MED GUIDE format (reference femhrt label)

Meeting Minutes

Date: November 17, 1999 **Time:** 1:00 PM - 2:00 PM **Place:** Parklawn; Room 17B-45

NDA: 20-323/S-021 **Drug Name:** Vivelle (estradiol transdermal system) 0.0375, 0.05, 0.75, 0.1 mg/day

Indication: Estrogen replacement therapy (ERT)

Sponsor: Novartis Pharmaceuticals Corporation.

Type of Meeting: Labeling and Status

FDA Lead: Dr. Shelley Slaughter

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Shelley Slaughter, M.D., Ph.D. – Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Phill Price, M.D. - Medical Officer, DRUDP (HFD-580)
Diane Moore – Regulatory Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Rajiv Agarwal, Ph.D. – Chemist, DNDC II @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Lisa Kammerman, Ph.D. - Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Mahboob Sobhan, Ph.D. – Statistical Reviewer, Division of Biometrics II (DBII) @ (HFD-160)
Lisa Stockbridge, Ph.D. - Regulatory Reviewer, Division of Drug Marketing, Advertising and Communication (DDMAC; HFD-42)

Meeting Objective: To discuss the labeling for Supplement 21 and the status of the reviews.

Discussion Points:
- Chemistry
  - the actual transdermal system should have a printed label which includes the tradename and the release rate of the patch; the certificate of analysis (COA) for the ink and other technical information regarding the procedure should be submitted to the NDA either to this supplement or to a subsequent chemistry supplement; if the materials are the same as for NDA 20-538, the data previously submitted to that NDA could be referenced
  - mock-up labeling for NDA 20-323 should be submitted for review
- Clinical Pharmacology and Biopharmaceutics
  - the sponsor has proposed revisions to the Clinical Pharmacology section of the label that are redundant
  - a review has been completed; a memo discussing the labeling will follow
- Clinical
  - newer estrogen products are now required to provide relevant clinical study data supporting the indications previously granted under estrogen class labeling; this product has the estrogen class

labeling indications but did not provide clinical data for some of the approved indications; this issue should be addressed by the sponsor in the near future

- in the **Clinical Studies** subsection, **Table 1** (Mean change from baseline in daily frequency of hot flushes for Vivelle compared to placebo) in study 1 (efficacy evaluable population N=209), the patients presented are evaluable patients which makes the data misleading; the data should reflect the intent-to-treat population to be statistically significant
- the Division has reanalyzed the data; Study 36 was powered sufficiently to demonstrate statistically that the 0.0375 mg dose beats placebo; Table 1 and Table 2 could be replaced by a table showing the results of Study 36 with the 0.0375 mg dose and placebo so that the lowest effective dose is depicted in the labeling; patients could be titrated to higher doses as needed as described in the text

Decisions Reached:

- eling
- cussed
- posed
- Patient Package Insert
- remain label)

- **Action Items:**

Item:	**Responsible Party:**	**Date Due:**
revise Clinical Studies section	Drs. Slaughter and Price	November 29, 1999
revise Biopharmaceutics section	Dr. Jarugula	November 29, 1999
convey comments to sponsor	Ms. Moore	November 30, 1999
schedule labeling meeting	Ms. Moore	upon receipt of revised sponsor labeling

/S/ 12/20/99
Signature, recorder

/S/ 12/21/99
Concurrence, Chair

Minutes of Teleconference

Date: November 2, 1999 **Time:** 11:30 AM - 12:00 PM **Place:** Parklawn; Room 17B-45

NDA: 20-323/S-021 **Drug Name:** Vivelle (estradiol transdermal system) 0.0375, 0.05, 0.75, 0.1 mg/day

Indication: Estrogen replacement therapy (ERT)

External Constituent: Novartis Pharmaceuticals Corporation

Type of Meeting: Guidance (Statistical)

FDA Lead: Dr. Maboob Sobhan **External Lead:** Ms. Lynn Mellor

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Phill Price, M.D. - Medical Officer, DRUDP (HFD-580)
Diane Moore - Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Mahboob Sobhan, Ph.D. – statistical reviewer, Division of Biometrics II (DBII) @ (HFD-160)

External Participants:
Lynn Mellor – Associate Director, Drug Regulatory Affairs, Novartis
Nero Gupta, M.D. – Clinician, Novartis
Eric Gibson – Statistician, Novartis

Meeting Objective: To request information on the intent-to-treat (ITT) population from Protocol 36.

Discussion Points:
- an analysis of the ITT population during the first treatment cycle was not provided in this submission; the location of the data is also not clearly delineated; the Division is requesting the sponsor provide the analysis or describe the location of the data in the submission
- the sponsor noted that three patients receiving Vivelle and seven patients receiving placebo had less than 10 days of data during the first 4-6 weeks of the first cycle; the sponsor felt that those patients did not meet the inclusion criteria in the last 10 days of Cycle One and should not be included in the analysis; the patients in the analyzed group were referred to as "acceptable patients"
- upon analysis of the data, it appears that the ITT patient population is not included in the analysis in Cycle One; all "acceptable patients" are not ITT patients
- two patients on placebo did not receive any drug and have no post-baseline measurements; one patient on active drug has no diary data from the last two weeks of Cycle One; these patients may be excluded from the ITT population
- in Module 1, Table 6.1.1, the numbers do not agree in the efficacy analysis for Cycle Three; for patients who do not have complete diary data, data from the last two full weeks of diary data can be averaged and used to carry forward as delineated out in the analysis report

- the sponsor is in the process of migrating all study data from an old computer system to an upgraded system; any reanalysis of data would take one month to complete; the study data for the ITT population may be obtainable from the submitted data in [redacted] using baseline data from that file

Decisions Reached:

- out of the 259 total patients, one patient in the Vivelle group and two patients in the placebo group can be excluded from the ITT analysis because no treatment had been given to them; the remainder that were not included in the analysis should be included and the data reanalyzed
- the FDA statistician will attempt to retrieve the data from the electronic file and perform an analysis of the data; if the data is not easily obtained, the sponsor will be requested to submit a reanalysis of the data for the ITT population
- additional detailed information regarding the location of the submitted data will be conveyed directly from the sponsor's statistician to the Agency statistician

- **Action Items:**

Item:	**Responsible Party:**	**Date Due:**
discuss exact location of data	Drs. Sobhan and Gibson	1 day
reanalyze submitted data	Dr. Sobhan	1-2 weeks

/S/ 11/19/99
Signature, recorder

/S/ 11/19/99
Concurrence, Chair

cc:
HFD-580
HFD-580/LRarick/MMann/SSlaughter/PPrice/TRumble/DMoore/LKammerman/ENevius/MSobhan

Concurrence:
TRumble 11.15.99/MSobhan 11.17.99/PPrice 11.18.99

Meeting Minutes

Date: October 27, 1999 **Time:** 11:00 – 11:30 AM **Place:** Parklawn; Rm. 17B-43

NDA: 20-323/S-021 **Drug Name:** Vivelle (estradiol transdermal system) 0.0375, 0.05, 0.75, 0.1 mg/day

Indication: Estrogen replacement therapy

Sponsor: Novartis Pharmaceuticals

Type of Meeting: 6-Month Status Meeting

FDA Lead: Ms. Diane Moore

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Phill Price, M.D. - Medical Officer, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Diane Moore - Project Manager, DRUDP (HFD-580)
Mahboob Sobhan, Ph.D. Pharmacokinetics reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB; HFD-160)
Wakel Kamp Barnes Monique, M.D., Ph.D., OCPB HFD 870
Lisa Kammerman, Ph.D. - Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

Meeting Objective: To discuss the status of NDA 20-323, Supplement 21 for the removal of the efficacy disclaimer for the low dose (0.3 mg dose) tablet for vasomotor symptoms currently in the labeling.

Background: The supplement was submitted on April 30, 1999. The User Fee Goal Date is March 2, 2000. The supplement was considered fileable by consensus of the reviewers on June 15, 1999. No official filing meeting was held.

Decisions Reached:

- Clinical
  - the Medical review is targeted for completion by the end of November 1999
  - safety is not an issue in this supplement because the 0.0375 mg/day dose is the studied dose in this supplement; higher doses are currently being marketed
  - although the original NDA included two studies intended to demonstrate safety and efficacy of all doses (Studies 1003 A and B), the first study (Studies 1003 A) was not powered adequately to demonstrate efficacy of the 0.0375 mg/day dose of estradiol at the 4-week time point; Protocol 036 was submitted to support the efficacy of the 0.0375 mg/day dose at 4 weeks in order to remove the restrictive language in the labeling
  - two tables have been requested from the sponsor using ITT and evaluable patients
- Statistics
  - the statistical review is targeted for completion by the end of November, 1999; additional data should be requested from the sponsor if not found in submitted SAS data

  - the treatment effect of the 0.0375 mg/day strength is two hot flushes at 4-weeks; the confidence interval (CI) has not been provided
  - no intent-to-treat (ITT) data was submitted for the first treatment cycle; this information is critical for the support of efficacy during the 4-week time point
- Pharmacology/Toxicology
  - no issues to be discussed; no review needed per Dr. Raheja for this supplemental application
- Chemistry and Manufacturing and Quality Control
  - [redacted]
- Clinical Pharmacology and Biopharmaceutics
  - the **CLINICAL PHARMACOLOGY** section has been reformatted; this should be reviewed according to the estrogen draft guidance

Action Items:

• Item	Responsible Person:	Due Date:
• request additional statistical data from sponsor	Ms. Moore and Dr. Sobhan	1-week
• request any additional labeling comments from sponsor	Ms. Moore	1 month
• convey comments to sponsor	Ms. Moore	1 month

/S/ 11/29/99

Signature, recorder

Post Meeting Addendum: A teleconference was held with Ms. Lynn Mellor, of Novartis and Dr. Sobhan and Ms. Diane Moore from the FDA at 3:00 PM on October 7 1999. The location of the data in the NDA supplement, from the first cycle, for the ITT population was requested. If the location of the data could not be clarified, the Division requested that VMS results for the first cycle be submitted.

Concurrence:

TRumble 11.15.99/MSobhan 11.17.99/LKammerman 11.19.99/PPrice, AParekh 11.22.99

Concurrence not received from MWakel Kamp Barnes

cc:
HFD-580
HFD-580/LRarick/MMann/SSlaughter/PPrice/TRumble/DMoore/AParekh/MSobhan
HFD-580/MWakel Kamp Barnes/LKammerman

Meeting Minutes

Date: June 15, 1999 **Time:** 3:00 PM **Place:** Parklawn; Rm. 17B-43

NDA: 20-323/S-021 **Drug Name:** Vivelle (estradiol transdermal system)

Indication: HRT

Sponsor: Novartis Pharmaceuticals

Type of Meeting: Filing Meeting

FDA Lead: Dr. Lisa Rarick

Meeting Recorder: Ms. Diane Moore

Meeting Objective: To discuss the Fileability of Supplement 21 to NDA 20-323 by Novartis for removal of the efficacy disclaimer for the low dose (0.3 mg dose) tablet for vasomotor symptoms currently in the labeling.

Background:
The supplement was submitted on April 30, 1999. The User Fee Goal Date is March 2, 2000

Decisions Reached:
- the clinical, chemistry, pharmacology, biometrics, biopharmaceutics reviewers agree that this supplement is fileable; no concerns were made known at this time
- the filing meeting was cancelled
- the labeling meeting is scheduled for 1:00 PM on November 10, 1999

/S/ 6/15/99
Signature, recorder

/S/ 6/15/99
Signature, Chair

Post Meeting Addendum:

cc:
HFD-580
HFD-580/LRarick/MMann/SSlaughter/PPrice/TRumble/DMoore/EDeguia/KMeaker/AParekh/SHaidar
HFD-580/TRumble/DMoore

Minutes of Teleconference

Date: April 19, 1999 **Time:** 5:30 - 5:35 PM **Place:** Parklawn; Ms. Moore's Office

NDA: 20-323 **Drug Name:** Vivelle (estradiol transdermal system)

Indication: Hormone replacement therapy (HRT)

External Constituent: Novartis Pharmaceuticals Corporation

Type of Meeting: Guidance

FDA Lead: Dr. Lisa Kammerman **External Lead:** Ms. Lynn Mellor

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Diane Moore - Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Lisa Kammerman, Ph.D. - Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

External Participant:
Lynn Mellor – Associate Director, Drug Regulatory Affairs, Novartis

Meeting Objective:
To discuss the proposal to submit Study 103A and 103B in tables showing Least Squares (LS) mean and arithemetic mean as part of the text of the clinical trial report in the proposed NDA supplement.

Background: It was agreed in the teleconference dated February 4, 1999, that the efficacy analysis, case report forms and data files for Protocol 36, could be submitted in SAS transport files.

Decisions Reached:
- the proposed case tabulations can be submitted in paper form rather than electronic form
- data listings are not required for the clinical trial reports
- the primary efficacy variable is the change from baseline in the number of moderate-to-severe hot flushes; the secondary efficacy variable is the severity of hot flushes
- the clinical trial reports should contain both LS mean and arithmetic mean
- safety analyses from the previously reviewed NDA will not be submitted

- **Action Items:** none

/S/ 5/14/99
Signature, recorder

/S/ for LAK
Concurrence, Chair

drafted:
cc:

Minutes of Teleconference

Date: February 4, 1999 **Time:** 2:00 - 2:30 PM **Place:** Parklawn; Ms. Moore's Office

NDA: 20-323 **Drug Name:** Vivelle (estradiol transdermal system)

Indication: Hormone replacement therapy (HRT)

External Constituent: Novartis Pharmaceuticals Corporation

Type of Meeting: Guidance

FDA Lead: Ms. Diane Moore **External Lead:** Ms. Lynn Mellor

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Diane Moore - Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

External Participant:
Lynn Mellor – Associate Director, Drug Regulatory Affairs, Novartis

Meeting Objective:
To convey decisions reached regarding the Phase 4 protocol submitted by Novartis for removal of efficacy disclaimer for the low dose (0.0375 mg dose) tablet for vasomotor symptoms currently in the labeling.

Background:
On March 24, 1994, the sponsor committed to perform a Phase 4 study (Protocol 36) to define the percentage of patients who receive relief of their vasomotor symptoms at the lowest dose (0.0375 mg). In order to support the removal of the restrictive language in the **Dosage and Administration** section of the Vivelle® labeling referring to the 0.0375 mg/day dosage having a delayed onset of efficacy, the sponsor plans to submit the following:

- a reanalysis of study 1003A (this was one of the two pivotal trials in the original NDA submission)
- the original integrated summary of efficacy (ISE) from the two previously submitted pivotal studies (Studies 1003A and 1003B) as paper copies (not individual protocols)
- efficacy analysis, case report forms and data files for Protocol 36, submitted in SAS transport files
- an integrated summary of safety (ISS) is not planned for submission, however, safety data from Protocol 36 will be included in the clinical trial report

Decisions Reached: (see attached)

- the study appears to be powered appropriately
- the proposed submission of the ISE and second analysis from the previous studies and data from Protocol 36 appear to be acceptable for a VMS indication for the 0.0375 mg dose
- the proposed formats for the electronic submissions are acceptable

- the proposed case tabulations are acceptable
- the proposed text in WORD is acceptable for the package insert, Protocol 36 and the new ISE
- the Clinical Pharmacology and Biopharmaceutics section of the label should be reformatted according to the new Estrogen Labeling Guidance; adhesion data can be submitted, but it will not be mandated until the estrogen labeling guidance has been finalized
- the submission containing the Phase 4 study and reanalysis of the two previously submitted studies would qualify as an efficacy supplement which would require ½ the NDA User Fee
- the teleconference scheduled for February 4, 1999, can be cancelled

- **Action Items:** none

S 3/5/99
Signature, recorder

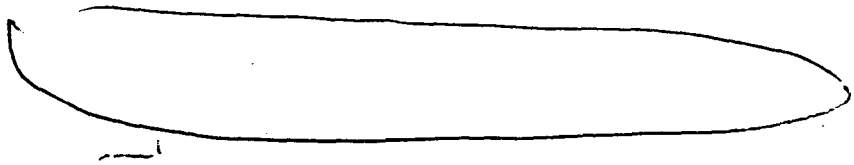
cc:
HFD-580
HFD-580/LRarick/MMann/SSlaughter/PPrice/TRumble/DMoore/EDeguia/KMeaker/AParekh/SHaidar
HFD-580/TRumble/DMoore

Concurrence:
TRumble 03.02.99

APPEARS THIS WAY
ON ORIGINAL

CONTENT/FORMAT ISSUES

We would like to obtain agreement on the following content related issues for the supplement:

- 

- CRF copies: will be provided for patients who dropped out due to an AE, had a clinically significant AE, or clinically significant lab abnormalities. Please not, there were no patient deaths. In addition, we propose not to submit CRFs that were previously submitted in the Original NDA, but cross reference to the previous submission (pertains to study 1003-A and 1003-B). CRF copies will be provided electronically according to the April 1998 FDA guidance document for regulatory submissions in electronic format – NDAs.

- Electronic data file submission: we propose to provide electronic data files that support the efficacy analyses for Protocol 036. The files will be provided in a SAS (version 6.12) transport format and will include important baseline, termination, and efficacy measurements.

- Case Report tabulations: for Protocol 036 data listings provided in an electronic document contain all the data collected on the CRFs and derived data used for analyses. The listings are sorted and presented by treatment, investigator center, patient, and visit for each domain (i.e., AEs, diary, vital signs, etc.). The termination listing is sorted by reason for termination. Laboratory data is sorted by investigator center, patient, and visit. We propose that these listings can be considered the case report tabulations and no electronic data files (SAS) be provided.

- Text files in Word 6.0 can be provided upon request

Meeting Minutes

Date: February 3, 1999 **Time:** 1:30 - 1:45 PM **Place:** Parklawn; Rm. 17B-43

NDA: 20-323 **Drug Name:** Vivelle (estradiol transdermal system)

Indication: HRT

Sponsor: Novartis Pharmaceuticals

Type of Meeting: Guidance

FDA Lead: Dr. Lisa Rarick

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Lisa Rarick, M.D. - Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Marianne Mann, M.D. - Deputy Director, DRUDP (HFD-580)
Shelley Slaughter, M.D., Ph.D. – Acting Team Leader, DRUDP (HFD-580)
Phill Price, M.D. - M.D. - Medical Officer, DRUDP (HFD-580)
Terri Rumble – Chief, Project Management Staff, DRUDP (HFD-580)
Diane Moore - Project Manager, DRUDP (HFD-580)
Eufrecina Deguia - Project Manager, DRUDP (HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Sam Haidar, R.Ph., Ph.D. - Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)
Kate Meaker, M.S. - Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

Meeting Objective:
To discuss the Phase 4 protocol submitted by Novartis for removal of efficacy disclaimer for the low dose (0.3 mg dose) tablet for vasomotor symptoms currently in the labeling.

Background:
On March 24, 1994, the sponsor committed to perform a Phase 4 study to define the percentage of patients who receive relief of their vasomotor symptoms at the lowest dose (3.28 mg).

Discussion Items:

- the proposed Phase 4 protocol appears to be adequate to demonstrate the amelioration of hot flushes for the 0.3 mg dose at three and four weeks
- the efficacy data from one previous study for this dose was questionable; another study showed positive results for this dose
- in this study, the vasomotor symptom relief appears to be significant to support efficacy of the 0.3 mg dose beginning at the third week
- the reanalysis of the less convincing study also appears to support the proposed efficacy of the 0.3 mg dose at three weeks

Decisions Reached:

- [redacted]
- the study is powered correctly
- the proposed submission of the ISE and second analysis is acceptable to support a potential VMS indication for the 0.3 mg dose
- the proposed electronic submissions are acceptable
- the proposed case tabulations are acceptable
- the proposed text in WORD is acceptable
- the Clinical Pharmacology and Biopharmaceutics section of the label should be reformatted according to the new Estrogen Labeling Guidance
- this submission would qualify as an efficacy supplement which would require ½ the NDA user fee

Action Items:

• **Item**	**Responsible Person:**	**Due Date:**
• convey comments to sponsor	Ms. Moore	3 days

/S/ 3/15/99
Signature, recorder

/S/ 3/16/99
Signature, Chair

Post Meeting Addendum:
In a telephone conversation between Lynn Mellor of Novartis and Diane Moore, dated February 4, 1999, the above comments were conveyed and it was agreed that the Telecon scheduled for February 4, 1999, could be canceled. It was further clarified that the data reanalysis was from the original data from study 1003-A in the original NDA submission (see teleconference minutes dated February 4, 1999).

2/19/99

cc:
HFD-580
HFD-580/LRarick/MMann/SSlaughter/PPrice/TRumble/DMoore/EDeguia/KMeaker/AParekh/SHaidar
HFD-580/TRumble/DMoore

Concurrence:
TRumble 02.22.99/KMeaker 02.24.99/MMann 02.25.99/EDeGuia 02.26.99
LRarick, SHaidar 03.01.99

Concurrence not received from SSlaughter/PPrice/AParekh

NDA 20-323/S-021
Vivelle® (estradiol transdermal system) 0.0375, 0.05, 0.75, 0.1 mg/day
Novartis Pharmaceutical Corporation

Advisory Committee Meeting Minutes

This supplemental application was not the subject of an Advisory Committee Meeting.

NDA 20-323/S-021
Vivelle® (estradiol transdermal system) 0.0375, 0.05, 0.75, 0.1 mg/day
Novartis Pharmaceutical Corporation

Federal Register Notices

This supplemental application was not the subject of any Federal Register Notices.

APPEARS THIS WAY
ON ORIGINAL

Novartis Pharmaceutical Corporation

Advertising Material

No advertising material has been submitted.

Food and Drug Administration
Rockville MD 20857

NDA 20-323/S-021

MAY - 4 1999

Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, New Jersey 07936-1080

Attention: Lynn Mellor, Associate Director
Drug Regulatory Affairs

Dear Ms. Mellor:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Vivelle

NDA Number: 20-323

Supplement Number: S-021

Date of Supplement: April 30, 1999

Date of Receipt: May 3, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on July 2, 1999 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Office of Drug Evaluation II
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

/S/

Terri F. Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic
Drug Products, HFD-580
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-323/S-021
HFD-580/Div. Files
HFD-580/CSO/MOORE

SUPPLEMENT ACKNOWLEDGEMENT